

We Claim:

1. In a method to modulate exogenous gene expression comprising contacting an ecdysone receptor complex comprising:

- a) a DNA binding domain;
- b) a ligand binding domain;
- c) a transactivation domain; and
- d) a ligand;

with a DNA construct comprising:

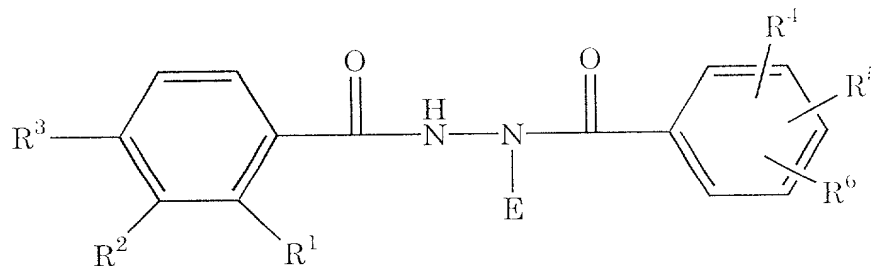
- a) the exogenous gene; and
- b) a response element;

wherein:

- a) the exogenous gene is under the control of the response element; and
- b) binding of the DNA binding domain to the response element in the presence of the ligand results in activation or suppression of the gene;

the improvement comprising:

selecting the ligand from a compound of the formula:



wherein:

E is a (C<sub>4</sub>-C<sub>6</sub>)alkyl containing a tertiary carbon or a cyano(C<sub>1</sub>-C<sub>5</sub>)alkyl

containing a tertiary carbon;

R<sup>1</sup> is H, Me, Et, i-Pr, F, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OH, OMe, OEt, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, SCN, or SCHF<sub>2</sub>;

R<sup>2</sup> is H, Me, Et, n-Pr, i-Pr, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, Ac, F, Cl, OH, OMe, OEt, O-n-Pr, OAc, NMe<sub>2</sub>, NEt<sub>2</sub>, SMe, SEt, SOCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>2</sub>H, COEt, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, OCF<sub>3</sub>, OCHF<sub>2</sub>, O-i-Pr,

SCN, SCHF<sub>2</sub>, SMe, NH-CN, or joined with R<sup>1</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy, a dihydrofuryl ring with the oxygen adjacent to a phenyl carbon, or a dihydropyryl ring with the oxygen adjacent to a phenyl carbon;

R<sup>3</sup> is H, Et, or joined with R<sup>2</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy, a dihydrofuryl ring with the oxygen adjacent to a phenyl carbon, or a dihydropyryl ring with the oxygen adjacent to a phenyl carbon;

R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are independently H, Me, Et, F, Cl, Br, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OMe, OEt, SMe, or SEt;

provided that:

a) when R<sup>1</sup> is Me and R<sup>2</sup> is OMe;

then R<sup>3</sup> is H; and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me, 3,5-di-OMe-4-Me, 3,5-di-Cl, or 3,5-di-F;

b) when R<sup>1</sup> is Me and R<sup>2</sup> is OEt;

then R<sup>3</sup> is H and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me, 3,5-di-OMe-4-Me, 3,5-di-Cl, 3,5-di-F, 2,4- or 2,5-di-F, 2,4- or 2,5-di-Cl ;

c) when R<sup>1</sup> is Et and R<sup>2</sup> is OMe or OEt;

then R<sup>3</sup> is H and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is:

i) 3,5-di-OMe-4-Me, 3,5-di-Cl, 3,5-di-F, 2,4- or 2,5-di-F, 2,4- or 2,5-di-Cl, 3-OMe, 2-Cl-5-Me, 2-Br-5-Me, 2-Cl, 2-Br, or 3-Me; or

ii) R<sup>6</sup> is H, R<sup>4</sup> is Me, and R<sup>5</sup> is Et, F, Cl, Br, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OMe, OEt, SMe, or SEt;

d) when R<sup>1</sup> is 1-Pr;

then R<sup>2</sup> is OMe, or OEt; R<sup>3</sup> is H; and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me;

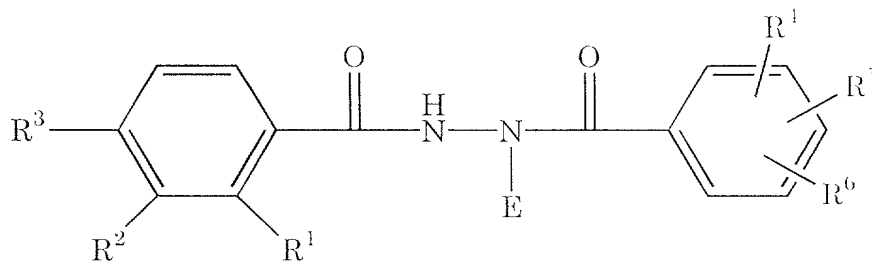
e) when R<sup>3</sup> is Et;

then R<sup>2</sup> is H, R<sup>4</sup> is F or Cl, and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me;

- f) when  $R^2$  and  $R^3$ , together with the phenyl carbons to which they are attached, form an ethylenedioxy ring;  
then  $R^1$  is Me or Et and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;
- g) when  $R^2$  and  $R^3$ , together with the phenyl carbons to which they are attached, form a dihydrofuryl or dihydropyryl ring;  
then  $R^1$  is Et and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;
- h) when  $R^1$  is formyl,  $CF_3$ ,  $CHF_2$ ,  $CHCl_2$ ,  $CH_2F$ ,  $CH_2Cl$ ,  $CH_2OH$ ,  $CH_2OMe$ ,  $CH_2CN$ ,  $CN$ ,  $C\equiv CH$ , 1-propynyl, 2-propynyl, vinyl,  $OH$ , cyclopropyl,  $CF_2CF_3$ ,  $CH=CHCN$ , allyl, azido,  $SCN$ , or  $SCHF_2$ ;  
then  $R^2$  is  $OMe$  or  $OEt$ ,  $R^3$  is  $H$ , and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me; and
- i) when  $R^2$  is Me, Et, n-Pr, i-Pr, formyl,  $CF_3$ ,  $CHF_2$ ,  $CHCl_2$ ,  $CH_2F$ ,  $CH_2Cl$ ,  $CH_2OH$ ,  $CH_2OMe$ ,  $CH_2CN$ ,  $CN$ ,  $C\equiv CH$ , 1-propynyl, 2-propynyl, vinyl, Ac, F, Cl,  $OH$ , O-n-Pr, OAc,  $NMe_2$ ,  $NEt_2$ , SMe, SEt,  $SOCF_3$ ,  $OCF_2CF_2H$ ,  $COEt$ , cyclopropyl,  $CF_2CF_3$ ,  $CH=CHCN$ , allyl, azido,  $OCF_3$ ,  $OCHF_2$ , O-i-Pr,  $SCN$ ,  $SCHF_2$ , SMe, or  $NH-CN$ ;  
then  $R^1$  is Et,  $R^3$  is  $H$ , and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me.

2. A method to modulate exogenous gene expression comprising contacting an ecdysone receptor complex comprising:

- a) a DNA binding domain;  
b) a ligand binding domain;  
c) a transactivation domain; and  
d) a ligand of the formula:



wherein:

E is a (C<sub>1</sub>-C<sub>6</sub>)alkyl containing a tertiary carbon or a cyano(C<sub>1</sub>-C<sub>5</sub>)alkyl containing a tertiary carbon;

R<sup>1</sup> is H, Me, Et, i-Pr, F, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OH, OMe, OEt, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, SCN, or SCHF<sub>2</sub>;

R<sup>2</sup> is H, Me, Et, n-Pr, i-Pr, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, Ac, F, Cl, OH, OMe, OEt, O-n-Pr, OAc, NMe<sub>2</sub>, NEt<sub>2</sub>, SMe, SEt, SOCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>2</sub>H, COEt, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, OCF<sub>3</sub>, OCHF<sub>2</sub>, O-i-Pr, SCN, SCHF<sub>2</sub>, SMe, NH-CN, or joined with R<sup>3</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy, a dihydrofuryl ring with the oxygen adjacent to a phenyl carbon, or a dihydropyryl ring with the oxygen adjacent to a phenyl carbon;

R<sup>3</sup> is H, Et, or joined with R<sup>2</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy, a dihydrofuryl ring with the oxygen adjacent to a phenyl carbon, or a dihydropyryl ring with the oxygen adjacent to a phenyl carbon;

R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are independently H, Me, Et, F, Cl, Br, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OMe, OEt, SMe, or SEt;

provided that:

a) when R<sup>1</sup> is Me and R<sup>2</sup> is OMe;

then R<sup>3</sup> is H; and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me, 3,5-di-OMe-4-Me, 3,5-di-Cl, or 3,5-di-F;

b) when R<sup>1</sup> is Me and R<sup>2</sup> is OEt;

then R<sup>3</sup> is H and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me, 3,5-di-OMe-4-Me, 3,5-di-Cl, 3,5-di-F, 2,4- or 2,5-di-F, 2,4- or 2,5-di-Cl ;

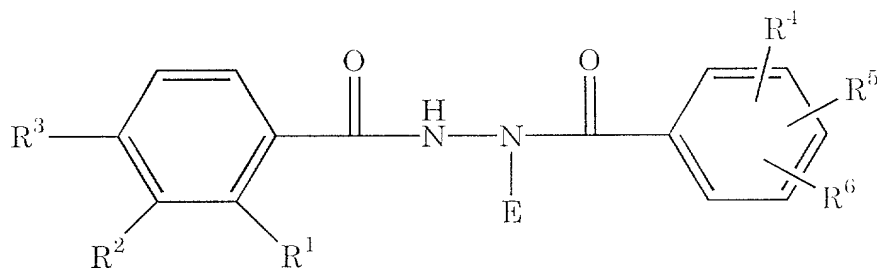
c) when R<sup>1</sup> is Et and R<sup>2</sup> is OMe or OEt;

then R<sup>3</sup> is H and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is:

- i) 3,5-di-OMe-4-Me, 3,5-di-Cl, 3,5-di-F, 2,4- or 2,5-di-F, 2,4- or 2,5-di-Cl, 3-OMe, 2-Cl-5-Me, 2-Br-5-Me, 2-Cl, 2-Br, or 3-Me; or
- ii) R<sup>6</sup> is H, R<sup>4</sup> is Me, and R<sup>5</sup> is Et, F, Cl, Br, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OMe, OEt, SMe, or SEt;
- d) when R<sup>1</sup> is i-Pr;  
then R<sup>2</sup> is OMe, or OEt; R<sup>3</sup> is H; and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me;
- e) when R<sup>3</sup> is Et;  
then R<sup>2</sup> is H, R<sup>4</sup> is F or Cl, and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me;
- f) when R<sup>2</sup> and R<sup>3</sup>, together with the phenyl carbons to which they are attached, form an ethylenedioxy ring;  
then R<sup>4</sup> is Me or Et and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me;
- g) when R<sup>2</sup> and R<sup>3</sup>, together with the phenyl carbons to which they are attached, form a dihydrofuryl or dihydropyryl ring,  
then R<sup>4</sup> is Et and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me;
- h) when R<sup>4</sup> is formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OH, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, SCN, or SCHF<sub>2</sub>;  
then R<sup>2</sup> is OMe or OEt, R<sup>3</sup> is H, and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me; and
- i) when R<sup>2</sup> is Me, Et, n-Pr, i-Pr, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, Ac, F, Cl, OH, O-n-Pr, OAc, NMe<sub>2</sub>, NEt<sub>2</sub>, SMe, SEt, SOCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>2</sub>H, COEt, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, OCF<sub>3</sub>, OCHF<sub>2</sub>, O-i-Pr, SCN, SCHF<sub>2</sub>, SOMe, or NH-CN;  
then R<sup>4</sup> is Et, R<sup>3</sup> is H, the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me;
- with a DNA construct comprising:
- a) the exogenous gene; and
- b) a response element;

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3. A method to modulate the expression of one or more exogenous genes in a subject, comprising administering to the subject an effective amount of a ligand of the formula:



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R<sup>3</sup> is H, Et, or joined with R<sup>2</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy, a dihydrofuryl ring with the

oxygen adjacent to a phenyl carbon, or a dihydropyryl ring with the oxygen adjacent to a phenyl carbon;

$R^1$ ,  $R^5$ , and  $R^6$  are independently H, Me, Et, F, Cl, Br, formyl,  $CF_3$ ,  $CHF_2$ ,  $CHCl_2$ ,  $CH_2F$ ,  $CH_2Cl$ ,  $CH_2OH$ , CN,  $C\equiv CH$ , 1-propynyl, 2-propynyl, vinyl, OMe, OEt, SMe, or SEt;

provided that:

a) when  $R^1$  is Me and  $R^2$  is OMe;

then  $R^3$  is H; and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me, 3,5-di-OMe-4-Me, 3,5-di-Cl, or 3,5-di-F;

b) when  $R^1$  is Me and  $R^2$  is OEt;

then  $R^3$  is H and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me, 3,5-di-OMe-4-Me, 3,5-di-Cl, 3,5-di-F, 2,4- or 2,5-di-F, 2,4- or 2,5-di-Cl ;

c) when  $R^1$  is Et and  $R^2$  is OMe or OEt;

then  $R^3$  is H and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is:

i) 3,5-di-OMe-4-Me, 3,5-di-Cl, 3,5-di-F, 2,4- or 2,5-di-F, 2,4- or 2,5-di-Cl, 3-OMe, 2-Cl-5-Me, 2-Br-5-Me, 2-Cl, 2-Br, or 3-Me; or

ii)  $R^6$  is H,  $R^4$  is Me, and  $R^5$  is Et, F, Cl, Br, formyl,  $CF_3$ ,  $CHF_2$ ,  $CHCl_2$ ,  $CH_2F$ ,  $CH_2Cl$ ,  $CH_2OH$ , CN,  $C\equiv CH$ , 1-propynyl, 2-propynyl, vinyl, OMe, OEt, SMe, or SEt;

d) when  $R^1$  is i-Pr;

then  $R^2$  is OMe, or OEt;  $R^3$  is H; and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;

e) when  $R^3$  is Et;

then  $R^2$  is H,  $R^1$  is F or Cl, and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;

f) when  $R^2$  and  $R^3$ , together with the phenyl carbons to which they are attached, form an ethylenedioxy ring;

then  $R^1$  is Me or Et and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;

g) when  $R^2$  and  $R^3$ , together with the phenyl carbons to which they are attached, form a dihydrofuryl or dihydropyryl ring;

then  $R^1$  is Et and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;

h) when R<sup>1</sup> is formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OH, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, SCN, or SCHF<sub>2</sub>;

then R<sup>2</sup> is OMe or OEt, R<sup>3</sup> is H, and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me; and

i) when R<sup>2</sup> is Me, Et, n-Pr, i-Pr, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, Ac, F, Cl, OH, O-n-Pr, OAc, NMe<sub>2</sub>, NEt<sub>2</sub>, SMe, SEt, SOCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>2</sub>H, COEt, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, OCF<sub>3</sub>, OCHF<sub>2</sub>, O-i-Pr, SCN, SCHF<sub>2</sub>, SOMe, or NH-CN;

then R<sup>1</sup> is Et, R<sup>3</sup> is H, the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me;

wherein the cells of the subject contain:

a) an ecdysone receptor complex comprising:

- 1) a DNA binding domain;
- 2) a binding domain for the ligand; and
- 3) a transactivation domain; and

b) a DNA construct comprising:

- 1) the exogenous gene; and
- 2) a response element; and

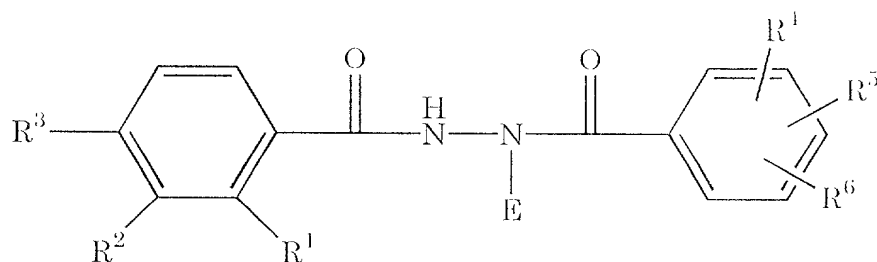
wherein:

- a) the exogenous gene is under the control of the response element; and
- b) binding of the DNA binding domain to the response element in the presence of the ligand results in activation or suppression of the gene.

4. A method for producing a polypeptide comprising the steps of:

- a) selecting a cell which is substantially insensitive to exposure to a ligand of the formula:





wherein:

E is a (C<sub>4</sub>-C<sub>6</sub>)alkyl containing a tertiary carbon or a cyano(C<sub>4</sub>-C<sub>5</sub>)alkyl containing a tertiary carbon;

R<sup>1</sup> is H, Me, Et, i-Pr, F, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OH, OMe, OEt, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, SCN, or SCHF<sub>2</sub>;

R<sup>2</sup> is H, Me, Et, n-Pr, i-Pr, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, Ac, F, Cl, OH, OMe, OEt, O-n-Pr, OAc, NMe<sub>2</sub>, NEt<sub>2</sub>, SMe, SEt, SOCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>2</sub>H, COEt, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, OCF<sub>3</sub>, OCHF<sub>2</sub>, O-i-Pr, SCN, SCHF<sub>2</sub>, SOMe, NH-CN, or joined with R<sup>3</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy, a dihydrofuryl ring with the oxygen adjacent to a phenyl carbon, or a dihydropyryl ring with the oxygen adjacent to a phenyl carbon;

R<sup>3</sup> is H, Et, or joined with R<sup>2</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy, a dihydrofuryl ring with the oxygen adjacent to a phenyl carbon, or a dihydropyryl ring with the oxygen adjacent to a phenyl carbon;

R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are independently H, Me, Et, F, Cl, Br, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OMe, OEt, SMe, or SEt;

provided that:

a) when R<sup>1</sup> is Me and R<sup>2</sup> is OMe;

then R<sup>3</sup> is H; and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me, 3,5-di-OMe-4-Me, 3,5-di-Cl, or 3,5-di-F;

- b) when  $R^1$  is Me and  $R^2$  is OEt;  
 then  $R^3$  is H and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me, 3,5-di-OMe-4-Me, 3,5-di-Cl, 3,5-di-F, 2,4- or 2,5-di-F, 2,4- or 2,5-di-Cl ;
- c) when  $R^1$  is Et and  $R^2$  is OMe or OEt;  
 then  $R^3$  is H and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is:  
 i) 3,5-di-OMe-4-Me, 3,5-di-Cl, 3,5-di-F, 2,4- or 2,5-di-F, 2,4- or 2,5-di-Cl, 3-OMe, 2-Cl-5-Me, 2-Br-5-Me, 2-Cl, 2-Br, or 3-Me; or  
 ii)  $R^6$  is H,  $R^4$  is Me, and  $R^5$  is Et, F, Cl, Br, formyl,  $CF_3$ ,  $CHF_2$ ,  $CHCl_2$ ,  $CH_2F$ ,  $CH_2Cl$ ,  $CH_2OH$ , CN,  $C\equiv CH$ , 1-propynyl, 2-propynyl, vinyl, OMe, OEt, SMe, or SEt;
- d) when  $R^1$  is i-Pr;  
 then  $R^2$  is OMe, or OEt;  $R^3$  is H; and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;
- e) when  $R^3$  is Et;  
 then  $R^2$  is H,  $R^1$  is F or Cl, and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;
- f) when  $R^2$  and  $R^3$ , together with the phenyl carbons to which they are attached, form an ethylenedioxy ring;  
 then  $R^1$  is Me or Et and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;
- g) when  $R^2$  and  $R^3$ , together with the phenyl carbons to which they are attached, form a dihydrofuryl or dihydropyryl ring;  
 then  $R^1$  is Et and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;
- h) when  $R^1$  is formyl,  $CF_3$ ,  $CHF_2$ ,  $CHCl_2$ ,  $CH_2F$ ,  $CH_2Cl$ ,  $CH_2OH$ ,  $CH_2OMe$ ,  $CH_2CN$ , CN,  $C\equiv CH$ , 1-propynyl, 2-propynyl, vinyl, OH, cyclopropyl,  $CF_2CF_3$ ,  $CH=CHCN$ , allyl, azido, SCN, or  $SCHF_2$ ;  
 then  $R^2$  is OMe or OEt,  $R^3$  is H, and the combination  $R^1$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me; and
- i) when  $R^2$  is Me, Et, n-Pr, i-Pr, formyl,  $CF_3$ ,  $CHF_2$ ,  $CHCl_2$ ,  $CH_2F$ ,  $CH_2Cl$ ,  $CH_2OH$ ,  $CH_2OMe$ ,  $CH_2CN$ , CN,  $C\equiv CH$ , 1-propynyl, 2-propynyl, vinyl, Ac, F, Cl, OH, O-n-Pr, OAc,  $NMe_2$ ,  $NEt_2$ , SMe, SEt,  $SOCF_3$ ,  $OCF_2CF_2H$ ,

COEt, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, OCF<sub>3</sub>, OCHF<sub>2</sub>, O-i-Pr, SCN, SCHF<sub>2</sub>, SMe, or NH-CN;

then R<sup>1</sup> is Et, R<sup>3</sup> is H, the combination R<sup>1</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me;

b) introducing into the cell:

1) a DNA construct comprising:

a) an exogenous gene encoding the polypeptide; and

b) a response element;

wherein the gene is under the control of the response element; and

2) an ecdysone receptor complex comprising:

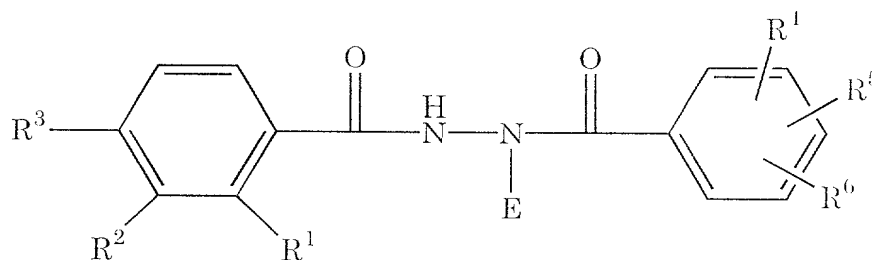
a) a DNA binding domain;

b) a binding domain for the ligand; and

c) a transactivation domain; and

c) exposing the cell to the ligand.

5. A method for regulating endogenous or heterologous gene expression in a transgenic organism comprising contacting a ligand of the formula:



wherein:

E is a (C<sub>4</sub>-C<sub>6</sub>)alkyl containing a tertiary carbon or a cyano(C<sub>3</sub>-C<sub>5</sub>)alkyl containing a tertiary carbon;

R<sup>1</sup> is H, Me, Et, i-Pr, F, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OH, OMe, OEt, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, SCN, or SCHF<sub>2</sub>;

R<sup>2</sup> is H, Me, Et, n-Pr, i-Pr, formyl, CF<sub>3</sub>, CHF<sub>2</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CH<sub>2</sub>OMe, CH<sub>2</sub>CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, Ac, F, Cl, OH, OMe, OEt, O-n-Pr, OAc, NMe<sub>2</sub>, NEt<sub>2</sub>, SMe, SEt, SOCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>2</sub>H, COEt, cyclopropyl, CF<sub>2</sub>CF<sub>3</sub>, CH=CHCN, allyl, azido, OCF<sub>3</sub>, OCHF<sub>2</sub>, O-i-Pr, SCN, SCHF<sub>2</sub>, SMe, NH-CN, or joined with R<sup>3</sup> and the

phenyl carbons to which  $R^2$  and  $R^3$  are attached to form an ethylenedioxy, a dihydrofuryl ring with the oxygen adjacent to a phenyl carbon, or a dihydropyryl ring with the oxygen adjacent to a phenyl carbon;

5  $R^3$  is H, Et, or joined with  $R^2$  and the phenyl carbons to which  $R^2$  and  $R^3$  are attached to form an ethylenedioxy, a dihydrofuryl ring with the oxygen adjacent to a phenyl carbon, or a dihydropyryl ring with the oxygen adjacent to a phenyl carbon;

10  $R^4$ ,  $R^5$ , and  $R^6$  are independently H, Me, Et, F, Cl, Br, formyl,  $CF_3$ ,  $CHF_2$ ,  $CHCl_2$ ,  $CH_2F$ ,  $CH_2Cl$ ,  $CH_2OH$ , CN,  $C\equiv CH$ , 1-propynyl, 2-propynyl, vinyl, OMe, OEt, SMe, or SEt;

provided that:

a) when  $R^1$  is Me and  $R^2$  is OMe;

then  $R^3$  is H; and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me, 3,5-di-OMe-4-Me, 3,5-di-Cl, or 3,5-di-F;

b) when  $R^1$  is Me and  $R^2$  is OEt;

then  $R^3$  is H and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me, 3,5-di-OMe-4-Me, 3,5-di-Cl, 3,5-di-F, 2,4- or 2,5-di-F, 2,4- or 2,5-di-Cl ;

c) when  $R^1$  is Et and  $R^2$  is OMe or OEt;

then  $R^3$  is H and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is:

i) 3,5-di-OMe-4-Me, 3,5-di-Cl, 3,5-di-F, 2,4- or 2,5-di-F, 2,4- or 2,5-di-Cl, 3-OMe, 2-Cl-5-Me, 2-Br-5-Me, 2-Cl, 2-Br, or 3-Me; or

ii)  $R^6$  is H,  $R^4$  is Me, and  $R^5$  is Et, F, Cl, Br, formyl,  $CF_3$ ,  $CHF_2$ ,  $CHCl_2$ ,  $CH_2F$ ,  $CH_2Cl$ ,  $CH_2OH$ , CN,  $C\equiv CH$ , 1-propynyl, 2-propynyl, vinyl, OMe, OEt, SMe, or SEt;

d) when  $R^1$  is i-Pr;

then  $R^2$  is OMe, or OEt;  $R^3$  is H; and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;

e) when  $R^3$  is Et;

then  $R^2$  is H,  $R^1$  is F or Cl, and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;

f) when  $R^2$  and  $R^3$ , together with the phenyl carbons to which they are attached, form an ethylenedioxy ring;

then  $R^1$  is Me or Et and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;

g) when  $R^2$  and  $R^3$ , together with the phenyl carbons to which they are attached, form a dihydrofuryl or dihydropyryl ring;

then  $R^1$  is Et and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;

h) when  $R^1$  is formyl,  $CF_3$ ,  $CHF_2$ ,  $CHCl_2$ ,  $CH_2F$ ,  $CH_2Cl$ ,  $CH_2OH$ ,  $CH_2OMe$ ,  $CH_2CN$ ,  $CN$ ,  $C\equiv CH$ , 1-propynyl, 2-propynyl, vinyl, OH, cyclopropyl,  $CF_2CF_3$ ,  $CH=CHCN$ , allyl, azido,  $SCN$ , or  $SCHF_2$ ;

then  $R^2$  is OMe or OEt,  $R^3$  is H, and the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me; and

i) when  $R^2$  is Me, Et, n-Pr, i-Pr, formyl,  $CF_3$ ,  $CHF_2$ ,  $CHCl_2$ ,  $CH_2F$ ,  $CH_2Cl$ ,  $CH_2OH$ ,  $CH_2OMe$ ,  $CH_2CN$ ,  $CN$ ,  $C\equiv CH$ , 1-propynyl, 2-propynyl, vinyl, Ac, F, Cl, OH, O-n-Pr, OAc,  $NMe_2$ ,  $NEt_2$ , SMe, SEt,  $SOCF_3$ ,  $OCF_2CF_2H$ , COEt, cyclopropyl,  $CF_2CF_3$ ,  $CH=CHCN$ , allyl, azido,  $OCF_3$ ,  $OCHF_2$ , O-i-Pr,  $SCN$ ,  $SCHF_2$ , SOMe, or NH-CN;

then  $R^1$  is Et,  $R^3$  is H, the combination  $R^4$ ,  $R^5$ , and  $R^6$  is 3,5-di-Me;

with an ecdysone receptor complex within the cells of the organism wherein

the cells further contain a DNA binding sequence for the ecdysone

receptor complex when in combination with the ligand and wherein

formation of an ecdysone receptor complex-ligand-DNA binding sequence

complex induces expression of the gene.

6. The method of Claim 2 wherein the ligand is of the specified formula and E is t-butyl;  $R^1$  is Me, Et, i-Pr, or F;  $R^2$  is OH, OMe, OEt, or joined with  $R^3$  and the phenyl carbons to which  $R^2$  and  $R^3$  are attached to form an ethylenedioxy or dihydrofuryl ring with the oxygen adjacent to a phenyl carbon;  $R^4$  is H, Et or joined with  $R^2$  and the phenyl carbons to which  $R^2$  and  $R^3$  are attached to form an ethylenedioxy or dihydrofuryl ring with the oxygen adjacent to a phenyl carbon; and  $R^4$ ,  $R^5$ , and  $R^6$  are independently Me, F, Cl,  $CH_2OH$ , or OMe.

7. The method of Claim 3 wherein the ligand is of the specified formula and E is t-butyl; R<sup>1</sup> is Me, Et, i-Pr, or F; R<sup>2</sup> is OH, OMe, OEt, or joined with R<sup>3</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy or dihydrofuryl ring with the oxygen adjacent to a phenyl carbon; R<sup>3</sup> is H, Et or joined with R<sup>2</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy or dihydrofuryl ring with the oxygen adjacent to a phenyl carbon; and R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are independently Me, F, Cl, CH<sub>2</sub>OH, or OMe.
8. The method of Claim 4 wherein the ligand is of the specified formula and E is t-butyl; R<sup>1</sup> is Me, Et, i-Pr, or F; R<sup>2</sup> is OH, OMe, OEt, or joined with R<sup>3</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy or dihydrofuryl ring with the oxygen adjacent to a phenyl carbon; R<sup>3</sup> is H, Et or joined with R<sup>2</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy or dihydrofuryl ring with the oxygen adjacent to a phenyl carbon; and R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are independently Me, F, Cl, CH<sub>2</sub>OH, or OMe.
9. The method of Claim 5 wherein the ligand is of the specified formula and E is t-butyl; R<sup>1</sup> is Me, Et, i-Pr, or F; R<sup>2</sup> is OH, OMe, OEt, or joined with R<sup>3</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy or dihydrofuryl ring with the oxygen adjacent to a phenyl carbon; R<sup>3</sup> is H, Et or joined with R<sup>2</sup> and the phenyl carbons to which R<sup>2</sup> and R<sup>3</sup> are attached to form an ethylenedioxy or dihydrofuryl ring with the oxygen adjacent to a phenyl carbon; and R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are independently Me, F, Cl, CH<sub>2</sub>OH, or OMe.
10. The method of Claim 2 wherein the ligand is of the specified formula and E is t-butyl, R<sup>1</sup> is Et, R<sup>2</sup> is OEt, R<sup>3</sup> is H, and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me.
11. The method of Claim 3 wherein the ligand is of the specified formula and E is t-butyl, R<sup>1</sup> is Et, R<sup>2</sup> is OEt, R<sup>3</sup> is H, and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me.

12. The method of Claim 4 wherein the ligand is of the specified formula and E is t-butyl, R<sup>1</sup> is Et, R<sup>2</sup> is OEt, R<sup>3</sup> is H, and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me.
13. The method of Claim 5 wherein the ligand is of the specified formula and E is t-butyl, R<sup>1</sup> is Et, R<sup>2</sup> is OEt, R<sup>3</sup> is H, and the combination R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is 3,5-di-Me.
14. The method of Claim 2 wherein the ecdysone receptor complex is a chimeric ecdysone receptor complex and the DNA construct further comprises a promoter.
15. The method of Claim 3 wherein the ecdysone receptor complex is a chimeric ecdysone receptor complex and the DNA construct further comprises a promoter.
16. The method of Claim 4 wherein the ecdysone receptor complex is a chimeric ecdysone receptor complex and the DNA construct further comprises a promoter.
17. The method of Claim 5 wherein the ecdysone receptor complex is a chimeric ecdysone receptor complex and the DNA construct further comprises a promoter.
18. The method of Claim 3 wherein the subject is a plant
19. The method of Claim 3 wherein the subject is a mammal.